Severe Congenital Protein C Deficiency

David Gelmont, MD
Baxter Healthcare Corporation

Definition of Severe Protein C Deficiency

- Homozygous or double heterozygous
- Very low Protein C level (below 20% activity) in an asymptomatic state

Epidemiology

- One in160-350,000 live births
- Only 17 subjects in the US are known to have severe congenital deficiency
- The expectation in the US is no more than 1-2 new patients per year based on our experience
- Similar number in the EU
- Most subjects die in utero

Disease Presentation

- Most subjects present at very young age (neonates and young babies)
- Many babies are born with cerebral infarcts and hemorrhage, blindness, infarcted kidneys, and multi-organ failure
- Neonate may develop Purpura Fulminans in the first few hours or days of life

Long lasting Complications of the disease

- Neurological sequelae (motor and cognitive dysfunction)
- Renal failure
- Amputations
- Blindness
- Multiple surgeries
- Major medical burden on society and healthcare systems

Baxter and super-orphan drugs

- The major reason for developing protein C was that a high level executive at Baxter was a great champion of this program
- In the current regulatory and re-imbursement climate Baxter most likely will be unable to develop future drugs for super-orphan indications

European Approval

On July 16, 2001 EMEA approved Ceprotin (protein C concentrate) under exceptional circumstances (conditional approval)

Ceprotin is the first plasma protein to be approved by the centralized procedure

EMEA SBA

"The approval was based on the results of efficacy analyses including twelve courses of short-term prophylaxis prior to surgery or invasive therapy and nine courses of long-term prophylaxis."

"The benefit of CEPROTIN is its anticoagulant effect."

EMEA SBA

"The CHMP, on the basis of quality, efficacy and safety data submitted, considers that the benefit/ risk ratio for CEPROTIN is favorable in the approved indication."

"The Marketing Authorization was granted under exceptional circumstances because the indications for which the medicinal product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the efficacy of the medicinal product."

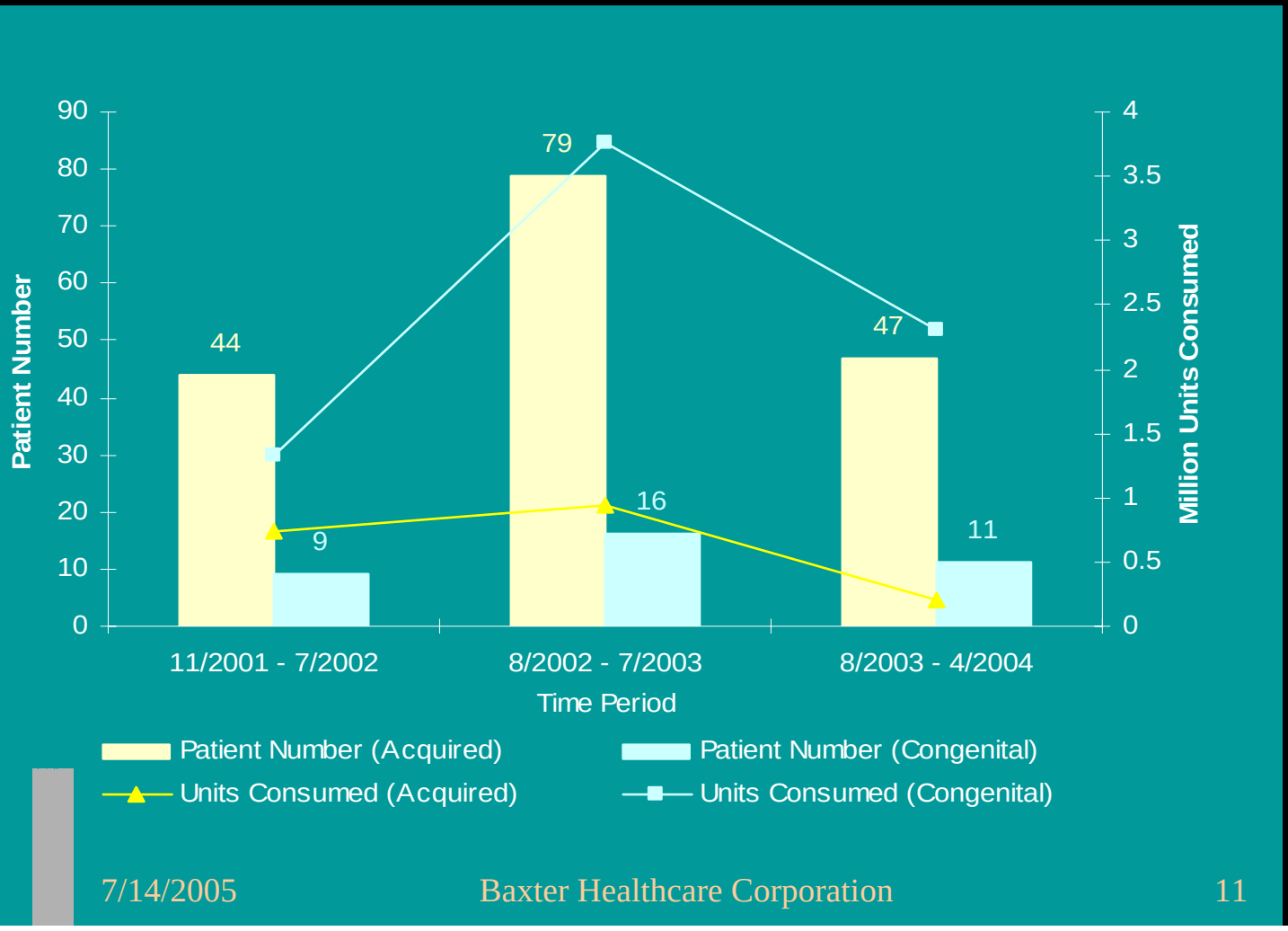
Post Marketing Commitments

1)“additional information from a prospective clinical study in patients with severe congenital protein C deficiency and

2) will report to the CHMP on the monitoring of all treatment courses of this medicinal product”

Full approval was granted upon completion of the prospective clinical study

Comparison by Patients (Acquired versus Congenital) and Protein C Units Consumed (CEPROTIN in European Union)



Obstacles in Conducting an Efficacy Study

- Small patient population (17 in US)
- Rare occurrence of events (in most of the subjects)
- Broad range of population age (one day old to 27 years old)
- No adequate control, and difficulties in blinding potential control arm
- Disease severity may inversely correlate with age

Phase-3 study

To demonstrate that Protein C Concentrate is safe and effective in subjects with congenital Protein C deficiency in the following indications:

a) **treatment of acute thrombotic episodes** such as purpura fulminans, coumarin-induced skin necrosis and other vascular thromboembolic events (Part-1)

b) **short-term thromboembolic prophylaxis** during surgical procedures, the postpartum period and the initiation of oral or parenteral anticoagulation (Part-2)

c) **long-term thrombotic prophylaxis** (Part-3)

Phase-3 Study

- We enrolled all known subjects in the US (18) with severe congenital protein C deficiency
- The study design attempted to satisfy (harmonize) both the EMEA and the FDA requirements
- We attempted to measure both clinical outcomes and bio-surrogates and compare them to a historical control
- The historical control data collection was extremely difficult

What did we learn in the process

- Because of the small number of eligible subjects, we wanted to include and keep every subject in the study and collect as much data as possible for each episode
- But, the protocol developed was cumbersome, complicated and difficult to execute
- The above resulted in multiple protocol deviations
- We concluded that we could not conduct a robust efficacy study

Super-orphan drugs
Suggestions for approval process

- Simplify the approval process globally
- Simplify clinical trials to consist of: PK study and phase-2/3 with Bio-surrogates as primary end-points (e.g. D-Dimer)
- Safety evaluation to be determined by rate of related AE's as a fraction of number of drug administrations (or total dose) and assessment of related SAE impact
- Employ descriptive statistics in pivotal study analysis
- Implement harmonization between the FDA & EMEA and other MOH

Super-orphan drugs
suggestions for post marketing commitments

- Establish patient registry to collect and publish data regarding safety and efficacy of drug
- Medical monitoring (Aralast home administration program)
- PMCs to be evaluated for discontinuation biannually
- Create FDA website for super-orphan drugs information